REMARKS

Claims 1-6, 22, 25 and 34 are currently pending. Claim 1 has been amended to more particularly clarify that the cyclooxygenase-2 inhibitor is selective. This amendment to claim 1 is supported by the specification and does not contain new matter.

Applicants will send another copy of the references detailed on the Information Disclosure Statement submitted to the Office on July 1, 2002, at a later date.

I. 35 U.S.C. §102 Rejection

Reconsideration is requested of the rejection of claim 1 and 22 under § 102(b) as anticipated by Deligeoroglou et al.[1]

Deligeoroglou et al. generally disclose causes, symptoms and potential treatment options for dysmenorrhea. The cited art discloses that the two principal pharmacotherapeutic agents employed in the treatment of primary dysmenorrehea are "oral contraceptives and non steroid anti-inflammatory drugs."[2] Deligeoroglou et al. also disclose that "lipoxygenase inhibitors and leukotriene antagonists, **in combination** with cyclooxygenase inhibitors,"[3] may be employed.

In contrast, claim 1 is directed toward a combination comprising a cyclooxygenase-2 **selective** inhibitor and a sex steroid. Within the context of the present invention, cyclooxygenase-2 **selective** inhibitors are defined as follows:

> ...agents that specifically inhibit a class of enzymes, cyclooxygenase-2, with less significant inhibition of cyclooxygenase-1. Preferably, it includes compounds that have a cyclooxygenase-2 IC_{50} of less than about 0.2 μM, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the

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[1] Deligeoroglou et al. (2000) Ann. New York Academy of Sciences 900:237-244.
[2] Id. at page 241.
[3] Deligeoroglou et al. (2000) Ann. New York Academy of Sciences 900:237-244.

compounds have a cyclooxygenase-1 IC_{50} of greater than about 1 μM, and more preferably of greater than 10 μM.[4]

Nowhere do Deligeoroglou et al. disclose the combination of a sex steroid with a cyclooxygenase-2 **selective** inhibitor as required by the combination of claim 1. Deligeoroglou et al.'s cyclooxygenase inhibitor is **not** a cyclooxygenase-2 **selective** inhibitor. In addition, Deligeoroglou et al. do not disclose the **combination** of claim 1. The reference discloses the combination of "lipoxygenase inhibitors and leukotriene antagonists, **in combination** with cyclooxygenase inhibitors,"[5] but not cyclooxygenase inhibitors in combination sex steroids, as required by claim 1. A claim is anticipated only if each and every element as set forth in the claim is described in a single prior art reference.[6] Because Deligeoroglou et al. do not disclose every element of claim 1, the reference does not anticipate claim 1. Claim 22 contains all of the elements of claim 1 and is not anticipated by Deligeoroglou et al. for all of the reasons stated with respect to claim 1 and by way of the additional requirements it introduces.

II. 35 U.S.C. §103 Rejection

Reconsideration is requested of the rejection of claims 1-6, 22, 25 and 34 under 35 U.S.C. §103(a) in view of Deligeoroglou et al., U.S. Patent No. 6,086,909 ('909 patent), and PDR (50th Ed., 1996).

Claim 1 is directed toward a combination comprising a cyclooxygenase-2 **selective** inhibitor and a sex steroid. The combination is employed to treat dysmenorrhea.

Deligeoroglou et al. generally disclose causes, symptoms and potential treatment options for dysmenorrhea. The cited art discloses that the two principal pharmacotherapeutic agents employed in the treatment of primary dysmenorrehea are

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[4] See specification at page 7.
[5] Deligeoroglou et al. (2000) Ann. New York Academy of Sciences 900:237-244.
[6] Verdegaal Bros. v. Union Oil Co. of Calif., 2 USPQ 2d 1051, 1053 (Fed. Cir. 1987). See MPEP §2131.

"oral contraceptives and non steroid anti-inflammatory drugs."[8] Deligeoroglou et al. also disclose that "lipoxygenase inhibitors and leukotriene antagonists, **in combination** with cyclooxygenase inhibitors"[9] may be employed. But as detailed in I. above, Deligeoroglou et al. do not disclose the use of **selective** cyclooxygenase-2 inhibitors and also do not suggest the use of **selective** cyclooxygenase-2 inhibitors in **combination** with sex steroids, as required by claim 1.

The '909 patent discloses a method for treating a "human female suffering from dysmenorrhea." In one embodiment, the '909 patent discloses administering a pharmaceutical agent selected from the group consisting of "nonsteroidal anti-inflammatory drugs, anti-prostaglandins, prostaglandin inhibitors, COX-2 inhibitors, local anesthetics, calcium channel blockers, potassium channel blockers, ß-adrenergic agonists, leukotriene blocking agents, smooth muscle inhibitors, vasodilators, and drugs capable of inhibiting dyskinetic muscle contraction."[10] But nowhere does the '909 patent disclose the use of a selective cyclooxygenase-2 inhibitor in **combination** with a sex steroid (or any other compound for that matter), as required by claim 1.

PDR generally discloses a list detailing a number of possible effects on menses resulting from the use of oral contraceptives. But nowhere does the reference disclose the use of oral contraceptives for the **treatment** of dysmenorrhea. Rather, PDR discloses that one of the non contraceptive benefits related to the use of oral contraceptives containing ethinyl estradiol may be the "decrease the incidence of dysmenorrhea." Moreover, nowhere does PDR disclose the use of oral contraceptives in combination with another compound for treatment of dysmenorrhea. And importantly, nowhere does PDR disclose the use of sex steroids in combination with selective cyclooxgygenase-2 inhibitors, as required by claim 1.

In the absence of any disclosure of the combination employed in claim 1, a *prima facie* case for obviousness is lacking.

The Office, however, asserts that it would have been obvious to combine two compositions (i.e., a cyclooxygenase-2 selective inhibitor and a sex steroid), each of

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[8] Id. at page 241.
[9] Deligeoroglou et al. (2000) Ann. New York Academy of Sciences 900:237-244.
[10] U.S. Patent No. 6,086,909, at summary of invention.

which is disclosed in the prior art to be useful for same purpose, in order to form a third composition that is used for the very same purpose (i.e., treatment of dysmenorrhea). But the cited art, taken singly or together, provide no basis for this conclusion.

Among the many compounds and classes of compounds disclosed by Deligeoroglou et al, PDR, and the '909 patent, none offer any guidance that would have motivated a skilled artisan to prepare the combination employed in claim 1. Deligeoroglou et al. disclose that "cyclooxygenase inhibitors" may be used, but state that they should be used in combination with "lipoxygenase inhibitors and leukotriene antagonists."[11] Moreover, in order to render a claim obvious, a prior art reference must disclose a process allowing **to make or obtain** the claimed compound before a *prima facie* case of obviousness can be made.[12] Nowhere does Deligeoroglou et al. disclose the use of **selective** cyclooxygenase-2 inhibitors in a manner that would allow a skilled artisan to "make or obtain" such a selective inhibitor. In fact, Deligeoroglou et al. disclose that "future research" is needed to "develop" cyclooxygenase inhibitors.[13] And even more revealing, all references cited by Deligeoroglou et al. regarding cyclooxygenase inhibitors were published before the discovery of the first human cyclooxygenase-2 **selective** inhibitor. For example, the cyclooxygenase-2 selective enzyme was not elucidated until the late 1980s and the first cyclooxygenase-2 selective inhibitor for humans, celecoxib, was not commercialized (i.e., available or obtainable) until 1999.[14] In contrast, the reference cited by Deligeoroglou et al. to support the use of cyclooxygenase inhibitors was published in 1982.[15] Clearly, the cyclooxygenase inhibitors contemplated by Deligeoroglou et al. are distinguishable from the cyclooxygenase-2 **selective** inhibitors required by claim 1.

If anything, Deligeoroglou et al. teach away from the combination employed in claim 1. The reference discloses that if "good relief of the dysmenorrhea" is not obtained by use of oral contraceptives alone, that prostaglandin synthetase inhibitors

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[11] Deligeoroglou et al. at 241.
[12] See, e.g., *In re Brown*, 329 F.2d 1006, 141 USPQ 245 (C.C.P.A. 1964); and *In re Hoeksema*, 399 F.2d 269, 158 U.S.P.Q. 596 (C.C.P.A. 1968).
[13] *Id.*
[14] See, A. Raz et al., (1990) Advances in Prostaglandin, Thromboxane, and Leukotriene Research, 20, 22-27; and J. Wallace et al., (1999) Current Opinion Anti-inflammatory Immunomodulatory Invest. Drugs, 1(2):100-110.
[15] Albin, P.E. and I.F. Litt. (1982) Pediatrics 70:516-521.

may also be administered. According to Deligeoroglou et al, "studies have shown that ibuprofen appears to have **the most favorable** risk/benefit ratio" of the prostaglandin synthetase inhibitors.[16] In addition, nowhere do Deligeoroglou et al. disclose that a cyclooxygenase inhibitor should be used in combination with an oral contraceptive. When considering the entire disclosure of Deligeoroglou et al., a skilled artisan may be motivated to combine ibuprofen and an oral contraceptive, but not a selective cyclooxygenase-2 inhibitor and a sex steroid, as required by claim 1.

Resort to either the '909 Patent or PDR does not cure the defect in the Office's obviousness rejection. The '909 patent discloses the use of cyclooxygenase-2 selective inhibitors for the treatment of dysmenorrhea, but fails to disclose or suggest any combination therapy, including the use of sex steroids. The PDR reference discloses that one of the non contraceptive benefits related to the use of oral contraceptives containing ethinyl estradiol may be the "decrease the incidence of dysmenorrhea." But the reference, analogous to the '909 patent, fails to disclose or suggest combination therapy. To properly establish a *prima facie* case of obviousness, the Office must consider the prior art in its entirety, **including portions that lead away from the claimed invention.**[17] Taken together, a skilled artisan empowered with the collective art of record, therefore, would not arrive at the combination of claim 1 without the disclosure of the Applicants' patent application.

In support of its position, the Office cites In re Kerkhoven.[18] In Kerkhoven, the inventor claimed a process for the production of particulate detergent compositions containing a mixture of anionic detergents and nonionic detergents.[19] The Examiner rejected the inventor's claims as obvious, stating the claims required no more than the mixing of two conventional spray-dried detergent compositions to form a third composition for the same purpose.[20] The CCPA affirmed the rejection, holding that it is *prima facie* obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, to form a third composition to be used for the

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[16]Deligeoroglou et al. at 241 (emphasis added).
[17]MPEP § 2141.02.
[18]626 F.2d 848, 205 USPQ 1069 (CCPA 1980).
[19]Id. at 848.
[20]Id. at 849.

same purpose.[21] According to the court, the motivation to combine the compositions "flow[ed] logically from their having been individually taught in the prior art."[22]

The instant situation involving claim 1 and the disclosures of the Deligeoroglou et al, '909 patent, and PDR may be distinguished from the facts of Kerkhoven. In Kerkhoven, there was no reason to expect that the combination of detergent compositions could act differently from the individual compositions comprising it, and thus, it would have been obvious to one skilled in the art to combine them for their additive effects as detergents. While this may be the case in the detergent arts, the same cannot be said about the pharmaceutical arts. Claim 1 discloses combinations that are intended to have a particular physiological effect, namely a treatment for dysmenorrhea. This combined physiological effect of the compounds would not have been obvious to one skilled in the art. A skilled artisan would have recognized that compounds known individually to be effective for relieving dysmenorrhea could possibly interfere with one another when combined, or in some way be ineffective in combination at tolerable doses. In either case, compositions comprising those compounds would not be effective to relieve dysmenorrhea. Moreover, when administering a pharmaceutical combination to a subject a number of physiological barriers must be overcome in order for the combination to be therapeutically effective *in vivo*. For example, the combination must be non toxic, bioavailable, (*e.g.*, able to reach its target) and have few side effects. In Kerkoven, the composition formed between the two detergents did not have to function in a physiological environment to be effective and thus, was not accompanied by the same degree of unpredictability as in the instant case. For all of these reasons, the present case is distinguishable from Kerkoven.

As stated by the Federal Circuit in Vaeck, "both the suggestion and the reasonable expectation of success must be founded in the prior art, not the applicant's disclosure."[23] Without a reasonable expectation that the combination of the two separate compounds recited in claim 1 (i.e., the cyclooxygenase-2 selective inhibitor

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[21] Id. at 850
[22] Id.
[23] In re Vaeck, 947 F.2d 488, 493 (Fed. Cir. 1991).

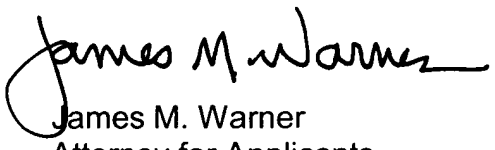
and sex steroid) would produce a composition that showed the physiological effect of treating dysmenorrhea, the second prong of the test laid out in Vacek has not been met.

For the foregoing reasons, the Office has failed to establish that claim 1 is *prima facie* obvious in view of the Deligeoroglou et al, '909 patent, and PDR. Claims 2-6, 22, 25 and 34 incorporate all of the claim 1 elements, and are likewise patentable over these references for the reasons stated with respect to claim 1 and by reason of the additional requirements they introduce.

III. Conclusion

In light of the foregoing, Applicants request entry of the claim amendments, withdrawal of the claim rejections, and solicit an allowance of the claims. The examiner is invited to contact the undersigned attorney should any issues remain unresolved.

Respectfully submitted,



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